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Alkynoate Synthesis *via* Vinylogous Reactivity of Rh(II) Carbenoids

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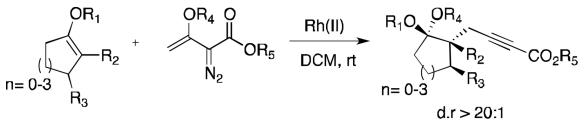
Abstract

A new rhodium carbenoid approach to access alkynoates has been developed. This transformation combines the addition of enol ethers at the vinylogous position of β-siloxy-substituted vinyldiazo derivatives and an unprecedented siloxy group migration to yield the products as single diastereomers.

Keywords

carbenoids; 2-alkynoate; siloxy-vinyldiazo; rhodium

2-Alkynoates represent a versatile class of synthetic intermediates in the field of organic synthesis[1] and are useful precursors to numerous biologically active compounds.[2] Despite significant interest from the synthetic community, facile incorporation of an alkynecarboxylate moiety is still an ongoing challenge. The difficulty associated with the direct alkylation of 2-alkynoates is due to their tendency to isomerize into the corresponding allenes under basic conditions, which are then prone to undergo conjugate addition.[3] In practice, commonly reported procedures require a multi-step reaction sequence.[4] A reasonably direct alternative approach to introduce the alkynecarboxylate group is the Nicholas reaction,[5] which allows the functionalization of propargylic sites with a variety of nucleophiles.[6] This approach requires the use of stoichiometric dicobalt reagents as well as the need to perform an oxidative decomplexation to regenerate the alkyne moiety following substitution. In this communication, we describe a new stereoselective approach that allows a straightforward access to highly functionalized alkyl 2-alkynoates by means of a rhodium-catalyzed transformation between silyl enol ethers and 3-siloxy-2-diazobutenoates [Eq. (1)].



(1)

The successful development of the aforementioned alkylation protocol is based on the discovery of an unusual transformation of rhodium-stabilized vinylcarbenoids. Transient vinylcarbenoids undergo a wide variety of synthetically useful reactions,[7] and their

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chemistry is particularly rich because they display electrophilic character at both the carbenoid site and the vinylogous position.[8] Especially versatile vinylcarbenoids are those derived from 3-siloxy-2-diazobutenoates. Reactions initiated at its carbenoid site have been used for stereoselective cyclopropanation[10] and the tandem cyclopropanation/Cope rearrangement,[11] leading to the synthesis of three-, five- or seven-membered carbocycles. The combination of siloxy α-diazoacetates with cinnamaldehydes offers access to complementary motifs.[12] More recently, the addition of nitrones to the vinylogous position of this carbenoid as well as a number of unusual transformations have been reported.[13] The key transformation behind the 2-alkynoate alkylation protocol also involves reaction at the vinylogous position of a vinylcarbenoid, but this is then followed by an unprecedented siloxy group migration.

We have had an extensive program to broaden the scope of substrates that undergo selective vinylogous addition over carbenoid-type transformations.[8] During these studies we discovered that the $Rh_2(esp)_2$[9]-catalyzed reaction of 1-(trimethylsiloxy)cyclohexene **1** with 3-siloxy-2-diazobutenoate **2** unexpectedly led to the formation of alkyne **3** as a single diastereomer in 53% yield (Scheme 1). The structure of compound **3** was unambiguously confirmed by single crystal X-ray diffraction.[13]

This reaction was intriguing not only because the formation of **3** occurred *via* vinylogous addition, but also because the disiloxyketal functional group arose from the migration of the OTBS group from the vinylcarbenoid to the cyclohexyl moiety. To the best of our knowledge, such migration is unprecedented in the carbenoid literature. In order to evaluate the stereospecificity of the transformation, the reaction between the siloxycyclohexene and β-siloxy-vinyldiazoacetate was repeated with the TBS and TMS substituents interconverted (Table 1, entry 1). The diasteromer to **3** was isolated in a highly stereoselective manner.

The scope of this transformation was then explored with a range of cyclic enol ethers. The reaction proceeded in moderate to excellent yields, and in all cases only a single diastereomer of the product was generated. With certain substrates, such as siloxyindene and siloxycyclobutene, the potentially competing products derived from carbenoid reactivity became apparent and resulted in lower isolated yields of the alkynoate products (Table 1, entries 5 and 7). We have demonstrated that increasing the size of the ester group in the vinylcarbenoid enhances the vinylogous reactivity.[8c,e] Indeed, when the reactions on these substrates were repeated using *t*-butyl 3-siloxy-2-diazobutenoates **5**, alkynoates **10** and **11** were isolated as the sole products in 84 and 98% yield, respectively (entries 6 and 8). The vinylogous reactions to the carbenoid derived from 3-butenediazoacetate **2** are also applicable to tetrasubstituted vinyl ethers, leading to the formation of alkynoates containing two adjacent quaternary centers (entries 9 and 10). The relative configuration of products **6–13** was assigned by analogy to alkynoate **3** since an equivalent migration is presumed to be involved in the formation of those compounds.

It is well established that donor/acceptor carbenoids are more selective than their acceptor-only homologs.[15] We have previously demonstrated that the reaction between donor/acceptor carbenoids and silyl enol ethers favors C—H insertion[16] or the combined C—H functionalization/Cope rearrangement[17] over cyclopropanation. In this particular alkynoate transformation we rationalize that the open/unsubstituted vinylogous position of the vinylcarbenoid is responsible for the vinylogous addition by the silyl enol ether. In addition, the use of sterically demanding nucleophiles, essentially tri- and tetra-substituted olefins, is certainly accountable for the enhancement of vinylogous reactivity.[8e,g] A plausible mechanism for the alkynoate formation is detailed in Scheme 2. Addition of the silyl enol ether to the unsubstituted γ-position of the activated β-siloxy-vinylcarbenoid would result in the formation of the zwitterionic intermediate **14**. Subsequent direct [1,4]-siloxy group

transfer or stepwise addition to the oxocarbenium ion via intermediate **15** followed by β-elimination would lead to the alkynoate product. Previous studies have shown that rhodium-stabilized β-siloxy-vinylcarbenoids have a strong preference for the *s-cis* conformation where the siloxy group points away from the "wall" of the catalyst.[17,18] We postulate that this conformational preference would be consistent with the rhodium carboxylate and the siloxy group adopting an anti-periplanar conformation which would then facilitate the β-elimination to afford the alkynoate product.

The X-ray structure of alkynoate **3** unambiguously shows that both the alkynyl side chain and the siloxy migrating group are on the same face of the cyclohexane. This led us to propose that the siloxy migration could be considered as an intramolecular transfer process that would preferentially occur in a suprafacial manner (path a vs b) as illustrated in Scheme 3.

Having established the basic propargylation method, studies were then conducted to determine the synthetic potential of the transformation. One obvious application would be to use the disiloxyketal as a carbonyl protecting group. Indeed the alkynoate products generated are readily converted into the corresponding ketones in high yield by simple treatment with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF). As demonstrated in Scheme 4, ketone **16** was isolated in 94% yield.

An exploratory study was then conducted to determine whether an enantioselective version of this transformation was feasible. Extensive experimentation revealed that the use of Rh_2(*S*-PTAD)$_4$ at −25 °C in TFT were the optimal conditions (see supporting information for further discussion on the optimized conditions). Representative examples are summarized in Table 2. Moderate levels of enantioinduction were observed, which demonstrated that the chiral catalyst was capable of limited facial selectivity. Interestingly the enantiomeric excess of the products increased proportionally with the size and flexibility of the ring (entries 1, 2 and 4).

The study was then extended to 3-substituted silyl enol ethers (Scheme 5). The $Rh_2(esp)_2$-catalyzed reactions of siloxy-vinyldiazoacetate **2** with **17–19** generated products of type **20–22** bearing three contiguous stereogenic centers as single diastereomers. The relative configuration of **20** was determined by 1D-NOE NMR studies and extended by analogy to compounds **21** to **22**. This result is consistent with a nucleophilic addition of the silyl enol ether *anti* to the 3-substituent, followed by intramolecular siloxy migration *syn* with respect to the alkyne moiety.

To demonstrate the practicality of this reaction, the above transformation was repeated using the enantioenriched silyl enol ether **(−)−19** (Scheme 6, 98% ee). As anticipated, product **(+)−22** was isolated as a single diastereomer with complete transfer of stereochemical information. As chiral 3-substituted silyl enol ethers, such as **(−)−19**, are readily obtained by asymmetric conjugate addition to an unsaturated carbonyl compounds,[19] this allows the propargylation procedure to be effectively used for the synthesis of highly enantioenriched products containing three contiguous stereogenic centers.

In summary, we have developed a method for the rapid access to highly functionalized 2-alkynoates in a single step using cyclic silyl enol ethers and siloxyvinylcarbenoids under Rh(II) catalysis in a highly diastereoselective manner. Further studies are in progress to extend this reaction, to acyclic enol ethers and to find systems that will give higher levels of asymmetric induction. These studies underscore the rich chemistry of rhodium-stabilized vinylcarbenoids, which has led to their broad application in a number of novel synthetic transformations.

Experimental Section

General procedure: A solution of siloxyvinyldiazoacetate (1.0 mmol, 2.0 equiv) in 6 mL of dried degassed DCM was added by syringe pump over 3 h at room temperature to a flame-dried 25 mL flask containing $Rh_2(esp)_2$ (7.7 mg, 0.02 equiv) and enol ether (0.5 mmol, 1.0 equiv) in 6 mL of dried degassed DCM under an argon atmosphere. The solution was stirred at room temperature for an additional 1 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (pentane/Et_2O) on silica gel to yield the product.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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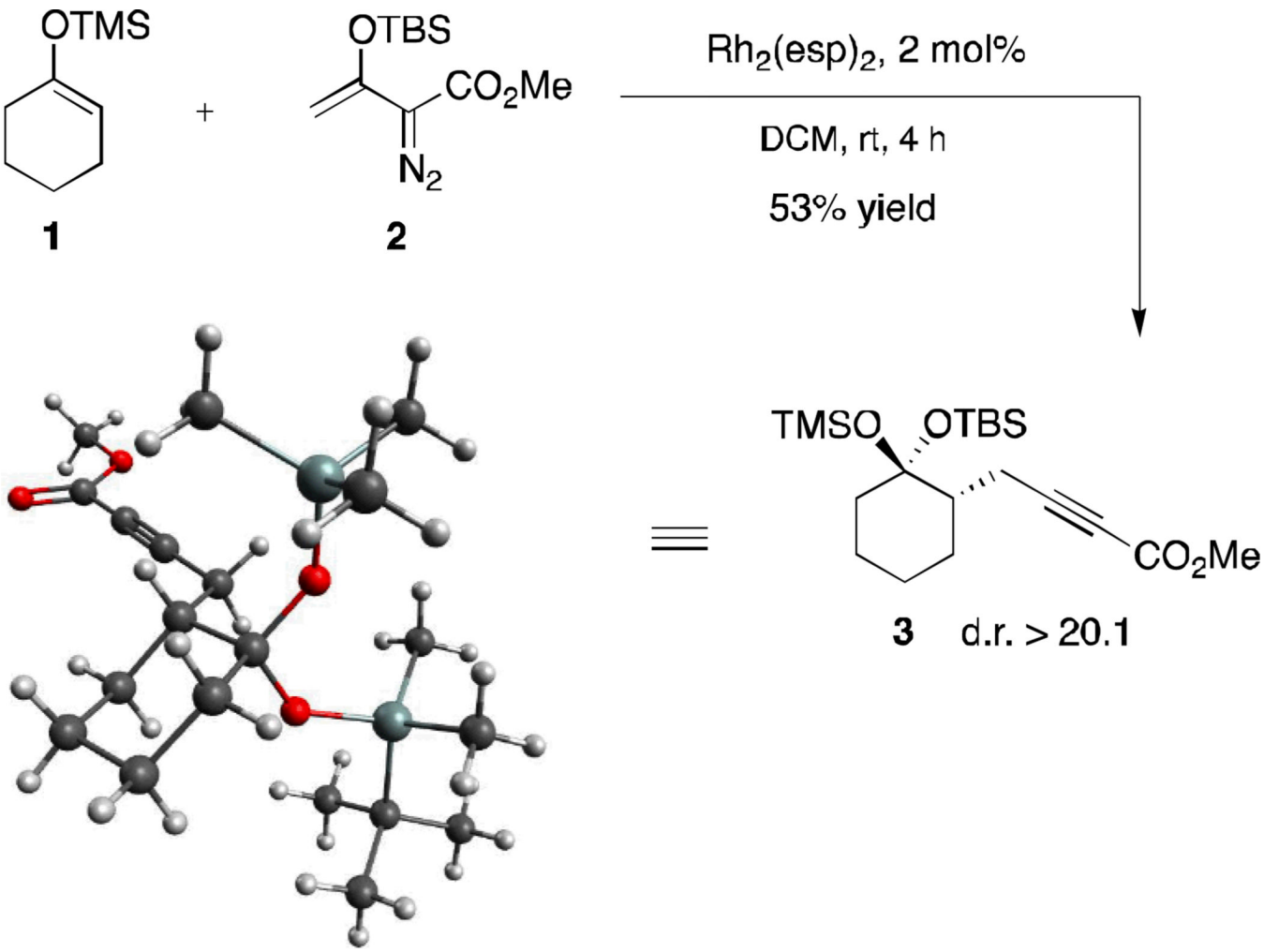
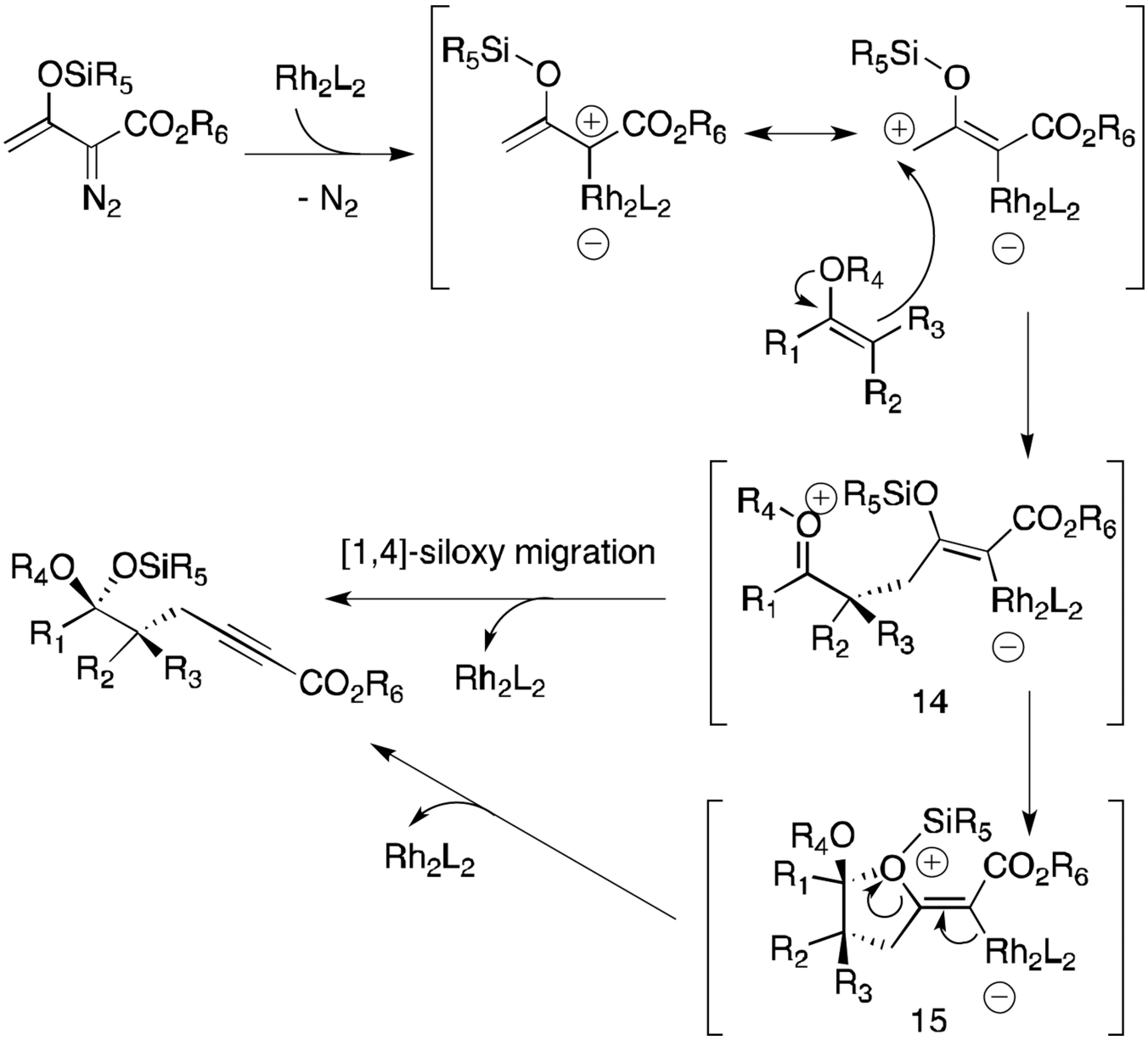
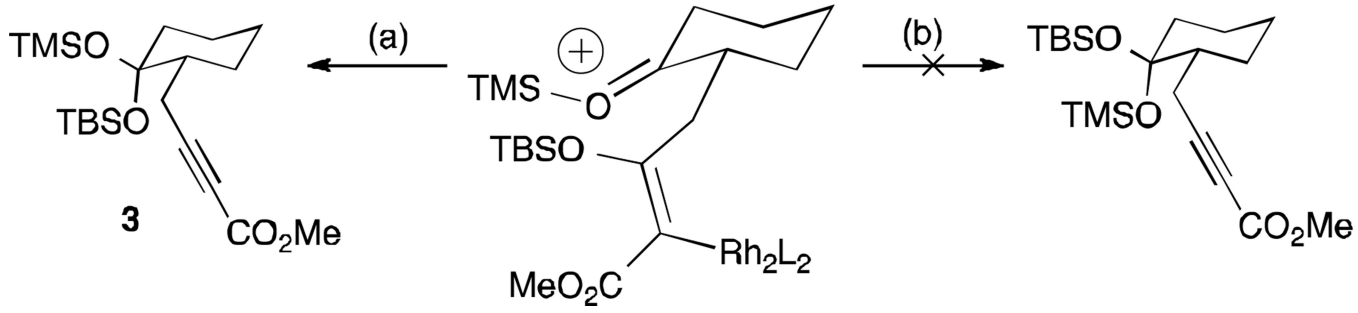


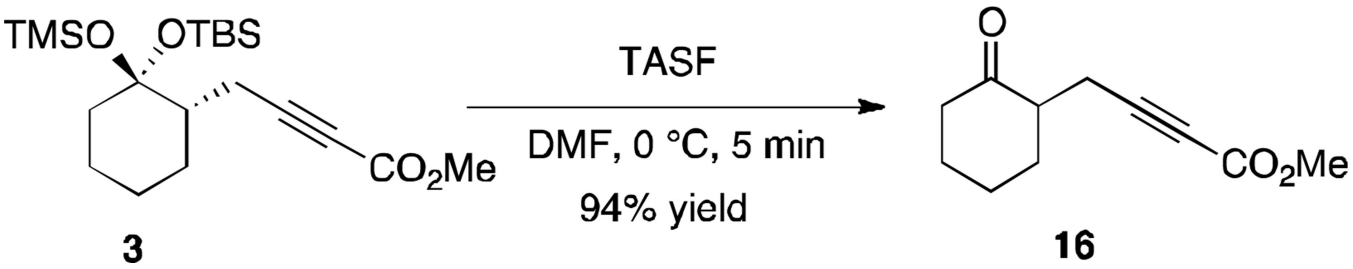
Scheme 1.
X-ray structure of product **3** formed from **2** and 1-(trimethylsiloxy)cyclohexene **1**



Scheme 2.
Proposed mechanism.

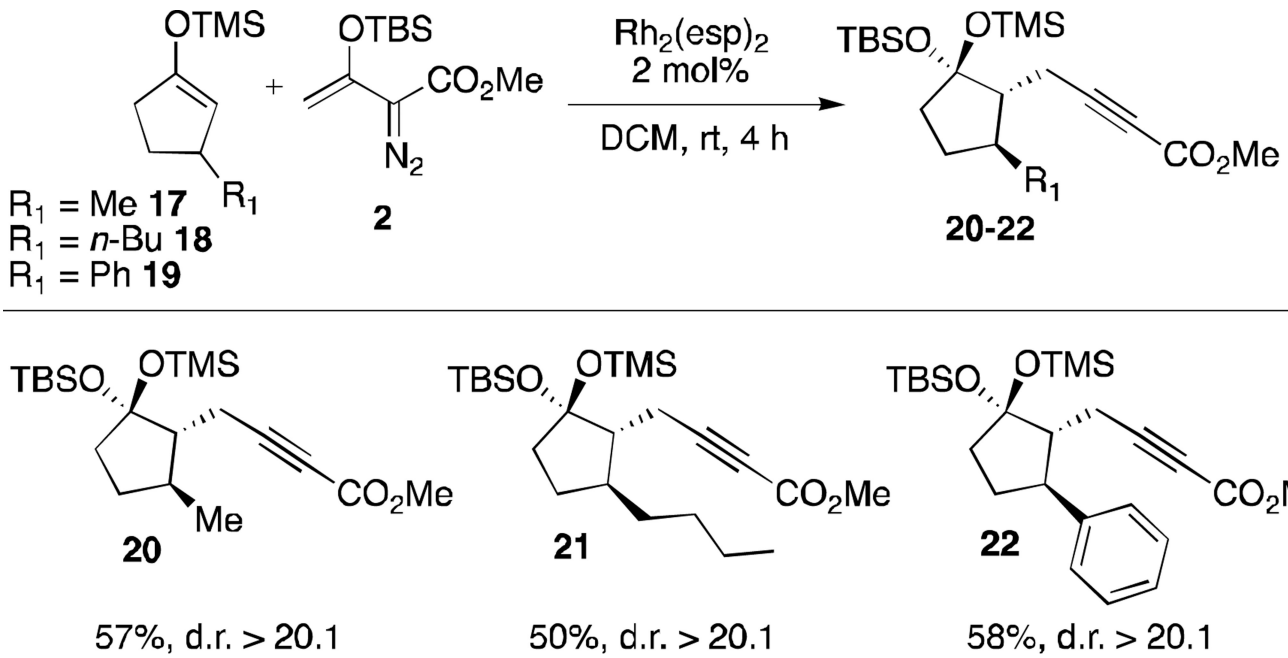


Scheme 3.
Rationale for the diastereoselectivity.

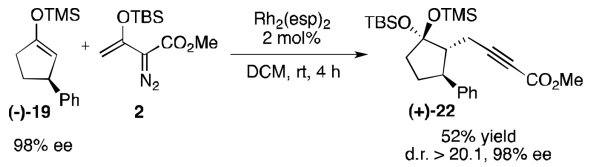


3 16

Scheme 4.
Access to 1,6-dicarbonyl compound **16**.



Scheme 5.
Scope of α-substituted silyl enol ethers.

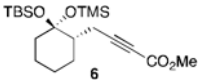
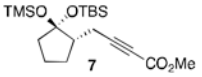
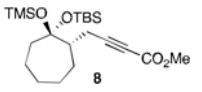
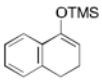
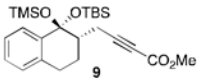
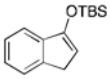
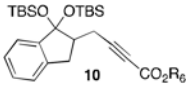
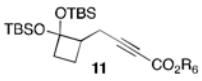
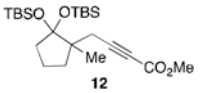
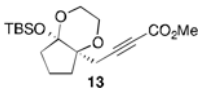


Scheme 6.
Alkynoate formation with conservation of enantioenrichment.

Table 1

Substrate scope.

R3: TBS, R4: Me **2**
R3: TMS, R4: Me **4**
R3: TBS, R4: *t*-Bu **5**

Entry	Substrate	Diazo	Product	Yield[a] [%]
1		**4**	 **6**	49[b]
2		**2**	 **7**	79[b]
3		**2**	 **8**	61[b]
4		**2**	 **9**	69[b]
5		**2**	 **10**	33[c]
6		**5**		84[d]
7		**2**	 **11**	51[c,e]
8		**5**		98[d]
9[f]		**2**	 **12**	56
10[f]		**2**	 **13**	53[b]

[a] Isolated yield.

[b] d.r. > 20:1.

[c] R_4=Me.

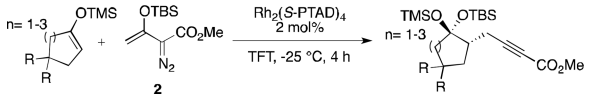
[d] R_4=*t*-Bu.

[e] Yield refers to the isolated alkynoate product which was separated from the cyclopropanated byproduct by column chromatography.

[f] Reaction was run at reflux.

Table 2

Asymmetric alkynoate synthesis.



Entry	R	n	Yield[a][%]	d.r.[b]	ee[c][%]
1	H	1	87	> 20:1	50
2	H	2	53	> 20:1	60
3	$O(CH_2)_2O$	2	49	> 20:1	46
4	H	3	69	> 20:1	70

[a] Isolated yield.

[b] Determined from ^{1}H NMR of the crude reaction mixture.

[c] Determined by chiral HPLC after hydrolysis of the disiloxyketal.